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Chapter16. DRUGS AND THE GASTROINTESTINAL TRACT

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Contents

DRUGS AND THE GASTROINTESTINAL TRACT

The subjects covered are the agents used for the control of acidity, prokinetics (which make the gut work faster) and anti-emetic (drugs that prevent nausea and vomiting). The agents used to treat diarrhoea, constipation and irritable bowel syndrome are also considered. Irritable bowel syndrome is fluctuations between diarrhea and constipation. Finally, drugs for inflammatory bowel disease are discussed.

16.1. AGENTS TO CONTROL ACIDITY

Dyspepsia (abdominal discomfort) is often triggered by particular foods (spicy, high fibre, fatty) or by eating too quickly or overeating. **Heartburn** (pyrosis) is painful, burning sensation in the throat (oesophagus), which is caused by the back-up of acid from stomach into the oesophagus leading to heartburn. Dyspepsia and heartburn are treated mainly with antacids, and if serious and ongoing, with proton pump inhibitors, and sometimes histamine H_2-receptor antagonists.

In **gastroesophageal reflux disease** (GERD, or gastro**o**esophageal to give GORD) there is heartburn and regurgitation. In GERD, the lower oesophageal sphincter is either weakened or opens too often. The sphincter defect can be caused by a hiatus hernia, obesity or pregnancy. If untreated, GERD can lead to cancers of the oesophagus. GERD is treated with antacids, proton pump inhibitors, and histamine H_2-receptor antagonists.

Peptic ulcers are due to an imbalance between mucosal defence factors and aggressive factors leading to excessive acid production, as discussed in Section 7.6.1. ***Helicobacter pylori*** infection is commonly associated with these ulcers. Treatment is with antibiotics to overcome the infection and with proton pump inhibitors to overcome the excessive acidity.

Ulcers can also be induced by the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) that are non-selective inhibitors of cyclooxygenase (COX) (e.g. aspirin). The ulcers are due to the removal of the cytoprotective prostaglandins. The treatment of NSAIDs-induced ulcers is proton pump inhibitors or misoprostol.

16.1.1 Antacids

Anti-acids (which are alkaline solutions) can be used to neutralise the acid in the stomach. There are lots of these available over-the-counter. Combinations of Mg^{2+} and Al^{3+} hydroxides provide a relatively fast and sustained neutralising capacity. Carbonates and bicarbonates also neutralise acid.

Mylanta is a mixture of aluminium hydroxide and magnesium hydroxide.

Gaviscon is a mixture of calcium carbonate, sodium bicarbonate and alignate, which is a viscous gum. Alignate helps protective mucus stick to the oesophagus, and this prevent acid damage.

As Mylanta and Gaviscone are available over-the-counter, it indicates that they are relatively **safe** agents. They are also cheap, compared to visiting a doctor and paying for a prescription. Antacids are cleared from stomach in about 30 minutes, which means that they may need to be taken frequently.

Antacids will **increase the pH of the stomach**, and altering gastric pH can affect dissolution, absorption and bioavailability of several drugs. In order to prevent this problem, it is best to avoid concurrent administration of antacids and other drugs. The suggestion is that there should be a two hour gap between taking antacids and other drugs.

With normal renal function, the modest accumulation of Al^{3+} from aluminium hydroxide is not a problem. However, in renal insufficiency, the increase levels of Al^{3+} can contribute to osteoporosis and proximal myopathy.

Antacids are used in the treatment of dyspepsia, heartburn, GERD, peptic ulcers and NSAIDs-induced ulcers. Antacids only relieve the symptoms; they do nothing to the underlying conditions.

16.1.2 Proton pump inhibitors (PPIs) and antibiotics for *Helicobacter pylori*

The most effective way to overcome excess acid, being produced from the parietal cells of the stomach, is to use proton pump inhibitors. This is because regardless of what is stimulating the acid secretion (histamine, gastrin and acetylcholine), inhibiting the proton pump will inhibit acid secretion. This makes the proton pump inhibitors the most effective inhibitors of acid secretion.

Omeprazole is the prototype proton pump inhibitor but there are other –prazoles in clinical use. The proton pump inhibitors are prodrugs, requiring activation in an acidic environment. To avoid activation of the omeprazole by the acid in the oesophagus and stomach, omeprazole is supplied as enteric-coated granules that dissolve only at an alkaline pH, which limits absorption to the intestine. Omeprazole is then carried in the blood stream until it is activated in the acid environment of the stomach.

The proton pump inhibitors inhibit the activity of some cytochrome P45O enzymes, and may decrease the clearance of benzodiazepines, phenytoin and warfarin, which will increase the concentration and increase the toxicity of these medicines. Proton pump inhibitors are used in the treatment of GERD and peptic ulcers, and in the prevention of NSAIDs-induced ulcers.

Up to 90% of peptic ulcers may be associated with *Helicobacter pylori* infections of the stomach leading to increased stimulation of acid secretion. *H. pylori* are Gram-negative rods. Unfortunately, single antibiotic regimens are ineffective as resistance has developed to *H. pylori.* Indeed, antibiotic resistance is preventing the elimination of *H. pylori.* The preferred combination of antibiotics used to kill *H. pylori* is **amoxicillin** and **clarithromycin**. These antibiotics are generally used in combination with a proton pump inhibitor. Besides reducing the acid secretion, the proton pump inhibitor enhances the effectiveness of pH-dependent antibiotics such as amoxicillin or clarithromycin.

16.1.3 Histamine H_2 receptor antagonists

Histamine H_2 receptor antagonists have previously been discussed (Chapter 16.3). An example of an H_2-receptor antagonist is **ranitidine**. Ranitidine is a relatively safe drug and is available over-the-counter in low doses. As histamine acting at the H_2-receptor is only one of the stimulants of acid secretion, H_2-receptor antagonists are only effective against this component. There are other stimulants of gastric secretion e.g. gastrin and acetylcholine, and H_2-receptor antagonists do not inhibit this secretion whereas proton pump inhibitors do. Thus, proton pump inhibitors are often preferred to H_2-receptor antagonists in peptic acidity conditions. H_2-receptor antagonists can be used for dyspepsia, heartburn, and GERD.

16.1.4 Misoprostol

Misoprostol has previously been discussed (Chapter 17.3.4). **Misoprostol** is a selective agonist at prostaglandin EP receptors. Misoprostol is active after oral administration, and is long lasting. Misoprostol is an effective inhibitor of acid secretion. The most frequent side

effect with misoprostol is diarrhoea, which occurs in about 30% of patients. The mechanism of the diarrhea is prostaglandin EP receptor-mediated stimulation of gut motility. Misoprostol also cause EP-receptor-mediated contractions of the uterus. Thus, misoprostol is contraindicated during pregnancy because it can cause abortion. Misoprostol is used to prevent mucosal injury caused by NSAIDs.

16.1.5 Sucralfate

After acid has damaged the lining of the intestine, pepsin can digest the mucosal proteins, and this contributes to mucosal erosion and ulceration. In an acidic environment, **sucralfate** produces a viscous, sticky gel. This gel sticks to ulcers to inhibit digestion of mucosal proteins. Antacids will prevent sucralfate from working, and should not be taken at the same time. By lining the intestine, sucralfate can prevent the absorption of some drugs (e.g. phenytoin, digoxin). To avoid this, sucralfate should be taken after other drugs. Sucralfate is occasionally used to treat ulcers.

16.2 PROKINETICS AND EMETICS

16.2.1 Introduction to prokinetics

Prokinetics enhance gastrointestinal motility and transit of material in gastrointestinal tract. Heartburn is due to the backup of acid from the stomach and oesophagus. The most common cause of heartburn is **Gastroesophageal reflux disease** (GERD or GORD). In GERD there is either a weakened lower oesophageal sphincter or the sphincter relaxes too frequently. In GERD, prokinetics prevent the heartburn by increase the motility in the oesophagus.

Gastroparesis is severely impaired emptying of stomach not caused by obstruction. The usual cause of gastroparesis is the loss of neural control as a result of diabetes. In gastroparesis, prokinetics increase the motility in the stomach, and this increases stomach emptying.

Irritable Bowel Syndrome (IBS) is intermittent cramps and constipation, with alternating periods of diarrhoea. Prokinetics are used in the constipation associated with irritable bowel syndrome.

16.2.2 Prokinetic agents

The contraction phase of peristalsis is due to release of acetylcholine from excitatory motor neurones. Prokinetic agents modify this release of acetylcholine. For instance, dopamine acts at D_2-receptors to inhibit the release of acetylcholine from the enteric nervous system. Antagonists at D_2-receptors will prevent this effect of dopamine, to increase the release of acetylcholine and increase gut motility.

Domperidone is a selective dopamine D_2-receptor antagonist that prevents the inhibitory effect of dopamine on acetylcholine release, which leads to an increased release of acetylcholine locally, which is prokinetic. Domperidone is used in GERD and gastroparesis.

5-Hydroxytryptamine (5-HT), acts at the 5-HT_4 receptor, to stimulate the enteric nervous system.

Metoclopramide is prokinetic by combining these two actions. Thus, metoclopramide acts as an antagonist at dopamine D_2-receptors, and an agonist at 5-HT_4-receptors, to stimulate the gastrointestinal tract. Metoclopramide is used in the treatment of GERD and gastroparesis.

16.2.3 Emesis with cytotoxic drugs and drugs for

One of the most serious causes of nausea and emesis (vomiting) is cytotoxic drugs (drugs that kill cells), such as the anti-cancer drugs. Some cytotoxic drugs are irritants to the gastro-intestinal tract, and this irritation involves 5-HT_3 receptors (Figure 16.1).

The other route to nausea and vomiting with cytotoxic drugs is when they are carried in the blood, to the chemoreceptor trigger zone in the area postrema of the central nervous system. There is also a neural input after gastrointestinal irritation to the chemoreceptor trigger zone. The chemoreceptor trigger zone or emetic centre has 5-HT_3-receptors, dopamine D_2 receptors, and muscarinic M_1-receptors (Figure 16.1), and consequently drugs that act at these receptors can modify nausea and vomiting.

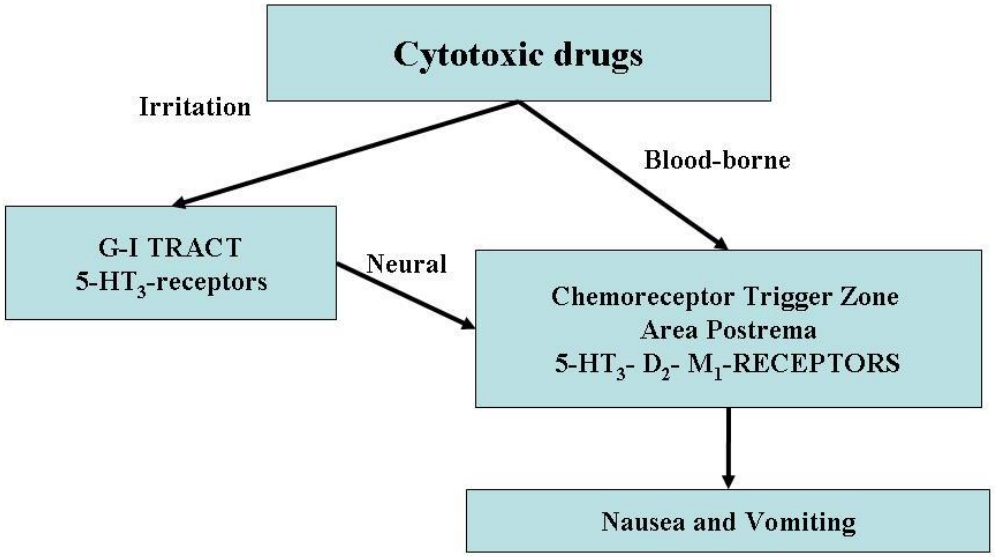

Figure 16.1 Nausea and vomiting with cytotoxic drugs (Copyright QUT, Sheila Doggrell)

The 5-HT_3-receptor antagonists, the –etrons, such as **ondansetron** (prototype) act at centrally- and peripherally 5-HT_3 receptors to inhibit emesis. The –etrons, such as ondansetron, are the most effective agents for treating chemotherapy-induced nausea and vomiting, but they are not effective in motion sickness, which involves a different pathway.

The dopamine D_2-receptor antagonists, **prochlorperazine** and **metoclopramide**, act as antagonists at the dopamine D_2-receptors in the chemoreceptor trigger zone to inhibit cytotoxic-induced emesis. These drugs used to be standard treatment for cytotoxic-induced emesis, but their use is declining as they are less effective than the 5-HT_3-receptor antagonists.

Prochlorperazine and metoclopramide are also used in the nausea and vomiting associated with pregnancy (morning sickness), where the underlying pathway remains to be clarified.

Substance P is a peptide neurotransmitter in the central nervous system that acts at NK_1-receptors. By stimulating NK-receptors, substance P has a role in emetic pathways, especially the emesis associated with chemotherapy. **Apepitant** is an antagonist at NK_1-receptors used to control chemotherapy-induced vomiting. Apepitant is not usually used as the first choice in preventing the emesis associated with chemotherapy, but can be used in

combination with ondansetron. Thus, when ondansetron is not effective alone, the addition of apepitant can increase the ability to inhibit the emesis caused by chemotherapy. Apepitant is metabolised by CYP3A4, and consequently can be involved in interactions with numerous drugs.

The glucocorticoids, especially **dexamethasone,** are used as anti-emetics to prevent emesis with cytotoxic drugs. The anti-emetic properties of the glucocorticoids were a seredipitous discovery. Thus, when dexamethasone was being used in chemotherapy, it was notices that there was less nausea and vomiting. As it was a chance discovery rather than a drug designed for specific target, the mechanism behind the anti-emetic effect of dexamethasone is not clear. The mechanism may be related to inhibition of the synthesis of prostaglandin E_2, as PGE_2 probably has a role on emesis. Dexamethasone is not generally used alone as an antiemetic, but is used with other antiemetics.

16.2.4 Motion sickness and drugs for

Drugs that are effective in the treatment of cytotoxic-induced emesis are not effective in motion sickness, indicating a different pathway is involved. Motion is monitored by the inner ear (the vestibular system), which has an input into the cerebellum, where histamine H_1-receptors and muscarinic M receptors are involved in controlling nausea and vomiting (Figure 16.2).

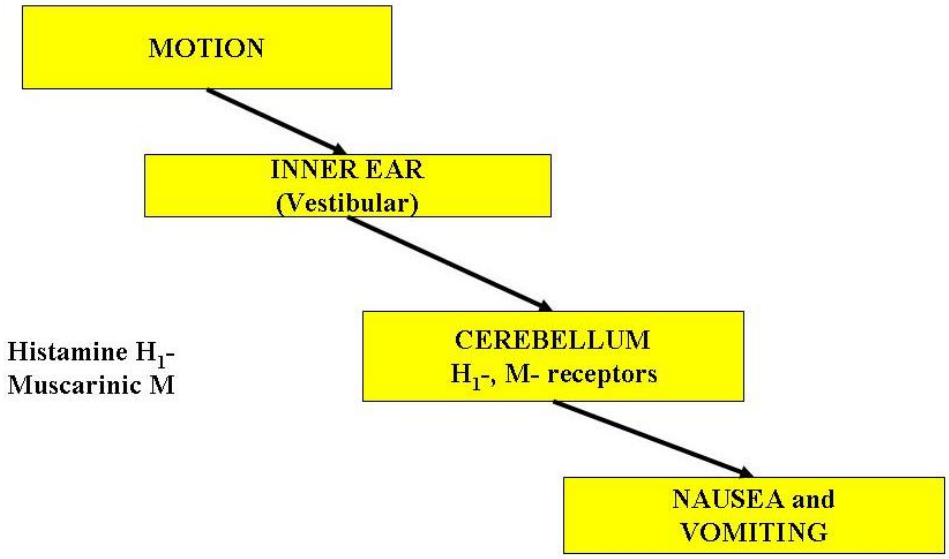

Figure 16.2 Motion sickness (Copyright QUT, Sheila Doggrell)

Thus, drugs that act at histamine H_1 receptors or muscarinic receptor can modify motion sickness. The histamine H_1-receptor antagonist **promethazine** crosses the blood-brain barrier to act at cerebellum histamine H_1-receptors to inhibit motion sickness. Promethazine also act as an antagonist at the cholinergic muscarinic receptors, which may contribute to effectiveness in preventing motion sickness.

The muscarinic receptor antagonist **scopolamine** is non-selective. Scopolamine crosses blood-brain barrier to act at the cerebellum M-receptor to inhibit motion sickness. Scopolamine is used as a transdermal patch to prevent motion sickness.

16.2.5 Post-operative emesis

Some of the drugs used for cytotoxic drug-induced or motion sickness-induced emesis are also useful in post-operative emesis. Thus, in post-operative emesis, the dopamine D_2

receptor antagonists (prochlorperazine, metoclopramide, the histamine H_1-receptor antagonist promethazine, the 5-HT_3-receptor antagonists (the –etrons, such as ondansetron) , and the muscarinic receptor antagonist scopolamine can all be useful.

16.3. AGENTS USED FOR DIARRHEA, CONSTIPATION, AND IRRITABLE BOWEL SYNDROME

Diarrhoea usually results from enteric infection and is short-lived and self-limiting, and does not usually require drug treatment. Other conditions that cause diarrhoea include malabsorption, which is associated with lactose intolerance and gluten malabsorption. Inflammatory bowel disease and immune disease are also causes of diarrhea, and these conditions require treatment.

Constipation is defined as having less than 3 stools per week. In constipation, the colon is absorbing too much water due to slow movement through colon.

Irritable Bowel Syndrome (IBS) is intermittent cramps and constipation, with alternating periods of diarrhoea. Thus, the drugs to treat diarrhoea and constipation are used in the treatment of irritable bowel syndrome.

16.3.1 Treatment for diarrhea

In the treatment of diarrhea, the replacement of fluids and electrolytes is a common treatment. In severe, prolonged bacterial infections, anti-bacterial drugs may be used.

When people abuse the opioid heroin, they become constipated. When the opioid morphine is used to relieve pain, it also causes constipation. Heroin and morphine stimulates **opioid μ-receptors** to decrease intestinal motility, which leads to increased absorption of water from the colon, and to constipation. This adverse effect in people with normal gut function has been used to develop an opioid agent suitable for use in diarrhea.

This agent is **loperamide**, which stimulates the gastrointestinal tract μ-receptors to be anti-diarrheal in subjects with diarrhea. Loperamide does not have any potential to be abused, as it is a poor penetrant of the central nervous system. Also, there are no central nervous side effects with loperamide. Loperamide is used in most forms of diarrhoea and in the diarrhea part of irritable bowel syndrome.

16.3.2 Treatment for constipation

The first treatment for constipation is lifestyle changes such as having a diet rich in fibre, decreasing the dietary fat intake, and increasing the intake of fluids but these fluids should not be diuretics as they promote water loss from the body. Daily exercise also stimulates peristalsis to overcome constipation.

In terms of agents used to overcome constipation, the old remedy of **castor oil** is effective but unpleasant, and potentially toxic, and therefore rarely used these days. Alternatives include bulk-forming laxatives, faecal softening agents, irritant laxatives and osmotic laxatives.

Dietary fibre is resistant to enzymatic degradation and presented to colon unchanged, and thus increasing bulk stimulates peristalsis. **Bulk-forming laxatives** mimic this effect. **Methylcellulose** (sold as Citrucel) is poorly fermented. Poorly fermented fibre attracts water to increase stool bulk, which stimulates peristalsis and eases movement along the

gastrointestinal tract. Bulk-forming laxatives are commonly used to prevent constipation in subjects prone to constipation.

Another example of a bulk-forming laxative is the commonly used **psyllium husk**. Psyllium husk is derived from the plantago seed and is in many commercial products for constipation (as Metamucil). It is fermented by the colonic bacteria to increase the bulk in the colon, and stimulate peristalsis. The fermentation also produces short chain fatty acids, which stimulate motility in the gastrointestinal tract (are prokinetic).

The **faecal softening agents** include **docusate** and **liquid paraffin**. Docusate acts like a detergent to allow water and fatty substances to mix with faecal material to soften it, and make it easier to pass stools. After the oral administration of docusate, there is an excretion of stools in 1-3 days. For a faster excretion, rectal administration of docusate can be used, and gives excretion of stools in 15 minutes.

Liquid paraffin is not dangerous after oral administration, as the absorption is minimal. The liquid paraffin stays in the tract, and coats stools to prevent loss of water. The major problem with using liquid paraffin as a faecal softening agent is that it can prevent the absorption of fat soluble vitamins (A, D, E and K), which will dissolve in the liquid paraffin and be excreted.

Agents that **stimulate or irritate the colon** to cause contraction include **bisacodyl** and **senna**. By stimulating colon contractions, bisacodyl and senna cause bowel evacuation in 6 to 12 hours. The faecal-softening agents and irritant laxatives are used in constipation.

The **osmotic laxatives** are poorly absorbed, and draw water toward them by osmosis. Subsequently, the osmotically-mediated water retention stimulates peristalsis. Examples of osmotic laxatives include glycerol, certain salts, and lactulose. **Glycerol** is an osmotic laxative, which is used rectally. After rectal administration, glycerol stimulates a bowel movement in an hour. Glycerol is used in constipation and constipation associated with irritable bowel syndrome.

The **salts** include milk of magnesia and Epsom salts. **Lactulose** is a non-digestible carbohydrate. Both salts and lactulose are taken orally, and in a low dose are laxative, but at high dose are cathartic (uncontrollable stools). As laxatives, the salts work in 6 to 8 hours, lactulose takes longer, 24 to 48 hours.

16.3.3 Opioid-induced constipation

The opioids e.g. morphine, are commonly used in the treatment of severe pain or pain associated with terminal disease. The analgesia is due to stimulation of opioid μ-receptors in the central nervous system. However stimulation of opioid μ-receptors on the gastrointestinal tract leads to constipation. Thus, constipation is a common side-effect of opioid use for pain relief or abuse for euphoria.

Methylnaltrexone is an antagonist at opioid μ-receptors. It can be administered orally, subcutaneously or intravenously. Methylnaltrexone does not cross the blood-brain barrier. Methynaltrexone antagonises the ability of opioids to cause constipation but, because it does not cross the blood-brain barrier. it does not antagonise the centrally-mediated analgesic effect of morphine. Methlynatrexone is used in combination with morphine to give pain

relief (due to the morphine) without the constipation (morphine-induced constipation prevented by methylnaltrexone).

16.4. DRUGS FOR INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease is distinct from irritable bowel disease/syndrome. Inflammatory bowel disease is chronic inflammation of small and large intestines, usually of unknown aetiology (cause).

Inflammatory bowel disease includes **Crohn's disease**, which can affect both the small and large bowel. In Crohn's disease, the inflammation is focal (localised) but can affect all layers of the bowel. The symptoms of Crohn's disease are severe abdominal pain, diarrhea (which may contain blood), vomiting, and weight loss.

Inflammatory bowel disease also includes **ulcerative colitis** (ulcers in the colon), which is confined to the colon and characterized by chronic, superficial inflammation. Ulcerative colitis always involves distal colon and extends continuously for a variable length proximally.

As the inflammation of inflammatory bowel disease is severe, it is not overcome by using a NSAID. Thus, stronger anti-inflammatory agents are required.

16.4.1 Mesalazine

Drugs related to the salicylates (i.e. aspirin), **5-aminosalicylates**, such as **mesalazine**, are used in the treatment of inflammatory bowel disease. Mesalazine inhibits both the cyclooxygenase pathway and lipooxygenase pathway, whereas the NSAIDs only inhibit the cyclooxygenase pathway. Thus, mesalazine inhibits the production of **prostaglandins** in the cyclooxygenase pathway, which have a relatively minor effect in inflammation. Mesalazine also inhibit the lipooxygenase pathway to reduce the levels of **leukotrienes**, which have a major role in inflammation.

Mesalazine is effective in mild or moderate active ulcerative colitis, but is a less successful treatment in severe ulcerative colitis. Mesalazine is also less useful in Crohn's disease. Mesalazine alone is absorbed before the colon, which reduces its effectiveness. Thus, mesalazine is used in enteric coated tablets to reduce any absorption from the stomach.

16.4.2 Glucocorticoids

Another major treatment for inflammatory bowel disease is the **glucocorticoids**. In addition to inhibiting the production of prostaglandins and leukotrienes by inhibiting phospholipase A_2 (as discussed in chapter 17.3), glucocorticoids have inhibitory effects on other components of inflammation, such as histamine, cytokines, and adhesion molecules. Adhesion molecules are required for white blood cells to adhere to the site of inflammation. **Prednisone** is an example of a glucocorticoid, which inhibits all these components of inflammation. Oral prednisone is the standard treatment for acute severe exacerbations of inflammatory bowel disease. Indeed, prednisone gives remission in most patients with ulcerative colitis and active Crohn's disease.

The main problem with glucocorticoids, such as prednisone, is systemic circulation leads to increasing and more severe side effects with time. Thus only short courses of treatment

should be used. With prolonged systemic treatment, prednisone causes the side effects of hypertension, hyperglycemia, an increased susceptibility to infection, osteoporosis, myopathy, behavioural disturbances, cataracts and more! Clearly, it is best to avoid long treatment with prednisone. Thus, prednisone is reserved for acute severe exacerbations of inflammatory bowel disease.

An alternative approach, if long term treatment with glucocorticoids is necessary is to use a glucocorticoid with extensive first pass liver metabolism to avoid some of the systemic side effects e.g. **budesonide**.

The weak glucocorticoid **hydocorticosterone** is used in enemas for a local effect in inflammation limited to the rectum (proctitis).

16.4.3 Infliximab

The cytokine tumour necrosis factor-alpha (TNF_α) has major role in Crohn's disease and ulcerative colitis. Thus, inhibitors of TNF_α are used in the treatment of Crohn's disease and ulcerative colitis. **Infliximab** is an antibody to TNF_α i.e. it binds to TNF_α and inactivates it. Infliximab is used in the treatment of moderate-to-severe Crohn's disease and moderate-to-severe ulcerative colitis. Infliximab is not active after oral administration and is given intravenously every 8 weeks to people with Crohn's disease or ulcerative colitis.